Amendments to the Specification:

Please replace paragraph 9 on page 2 with the following rewritten paragraph:

In a further embodiment, the levels of the gene expression products (proteins) can be monitored in various body fluids, including, but not limited to, blood plasma, serum, lymph, urine, stool and bile, or in biopsy tissues. This expression product level can be used as surrogate markers for early diagnosis of CR and can provide indices of therapy responsiveness. An example is e.g. the protein encoded by the Connective Tissue Growth Factor (GENBANK® ~~GenBank~~ accession number X78947).

Please replace the last paragraph on page 9 directly under the heading Homogenate pre-filtration and RNA extraction with the following rewritten paragraph:

Pre-filtration of the homogenate and RNA extractions are performed by the ABI 6700 BIOROBOT® ~~Biorobot~~ workstation (Applied Biosystems, USA). Tissue homogenates are filled into the wells of a 96-deep-well plate, and placed in the filtrate position of the 6700 workstation. A tissue pre-filter tray is placed into the purification carriage and locked into position. The instrument door is closed, and the workstation software is launched.

Please replace the first paragraph on page 10 with the following rewritten paragraph:

The RNA extraction procedure includes a sample transfer step, a filtration step, a washing step, and an elution step. The sample transfer step, in which the pre-filtered homogenate is transferred from the 96 deep-well plate to the RNA purification tray includes a primary transfer of 550 µl solution. Before the second transfer, 150 µl homogenization buffer (Applied Biosystems lysis buffer/PBS 1:1) is added to each well in the deep-well plate, mixed three times and then 150 µl are transferred from there to the purification tray. The filtration step is carried out by applying a vacuum pressure of 80% for 180 seconds. The washing steps are performed as follows:

Step 1: washing solution 1, 400 µl, vacuum pressure 80% for 180 seconds, two times;

Step 2: washing solution 2, 500 µl, vacuum pressure 80% for 180 seconds, once;

Step 3: washing solution 2, 300 µl, vacuum pressure 60% for 120 seconds, two times.

A pre-elution vacuum of 90% pressure is applied for 300 seconds. Hereafter the elution step is performed by the addition of 120 µl elution solution (Applied Biosystems), and the application of a 100% vacuum-pressure for 120 seconds. The RNA samples are collected in 96-well plates (Applied Biosystems). The eluates are split into two aliquots of equal volume. One aliquot is stored at - 80°C, the other aliquot is used for RNA amplification and GENECHIP® ~~GeneChip~~ analysis.

Please replace the first paragraph on page 11 with the following rewritten paragraph:

All enzymes and buffers for the amplification procedure are purchased from Invitrogen, Inc. (Carlsbad, CA, USA) unless explicitly mentioned. 10ml total RNA are incubated with 10 pmol T7-polydT primer [5'-GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG$(T)_{24}$] ~~SEQID.:1~~ SEQ ID NO:1, (Genset, Inc.) in a volume of 11µl at 70°C for 10 minutes, then at 42°C for 5 minutes. The first strand reaction is carried out in a volume of 20µl by the addition of 200 units SUPERSCRIPT® ~~SuperScript II~~ in the presence of first strand buffer, 10 mM DTT, 0.5 mM dNTP mixture, and 1µl RNase inhibitor (Ambion, Inc.) with a 42°C-incubation for 1hr. The second strand synthesis is performed in 150 µl with 40 units E.coli DNA polymerase I in 1x second strand buffer, 0.2 mM dNTPs, 10 units E.coli DNA ligase and 2 units RNaseH. After a 2-hour incubation at 16°C, the double-stranded DNA is blunt-ended by the addition of 8 units T4 DNA polymerase for 10 minutes at 16°C. The double-stranded DNA product is purified with a QIAQUICK® ~~QIAquick~~ PCR purification kit (Qiagen) and eluted in 50 µl elution buffer. For only one round of amplification the volume of the eluate is reduced to dryness under vacuum, resuspended in 22 µl nuclease-free water, and then used in the RNA labelling reaction as described below. For additional rounds of amplification, the eluate is reduced to dryness under vacuum, resuspended in 8 µl nuclease-free water, and subjected to an in-vitro transcription reaction with the Ambion MEGASCRIPT® ~~MEGAscript~~ kit, following the manufacturer's instructions for a 20 µl reaction volume. After a 3-hour incubation at 37°C the RNA is purified with the RNEASY® ~~RNeasy~~ kit system (Qiagen). The RNA is eluted in 30 µl RNase free water, reduced to dryness under vacuum and resuspended in 11 µl nuclease-free water.

Please replace the second paragraph on page 11 with the following re-written paragraph:

The second round of RNA amplification started with the addition of 1µl 0.1 mg/ml random hexamer primers followed by a 10-minute incubation at 70°C. The reaction mixture is chilled on ice and then incubated at room temperature for 10 minutes, at which point the first strand synthesis reaction is started by the addition of 200 units SUPERSCRIPT® ~~SuperScript II~~, 20 units RNase Inhibitor, 0.5 mM dNTPs and 10mM DTT in the presence of first strand reaction buffer. The mixture is incubated at 37°C for 1hour. A 20-minute RNase H treatment (2 units) at 37°C lead to the degradation of the residual RNA. RNase H is heat-inactivated at 94°C for 2 minutes and the mixture is chilled on ice. The second-strand synthesis is initiated by the addition of 100 pmol T7-polydT primer (see above) and incubation at 70°C for 5 minutes, followed by 42°C for 10 minutes. The second-strand synthesis is performed as described above, and the cDNA is purified with the QIAQUICK® ~~QIAquick~~ PCR purification kit (Qiagen). If this is the final

round of amplification, the volume of the eluate is reduced to dryness under vacuum and resuspended in 22 µl nuclease-free water, followed by an in-vitro RNA labeling procedure (see below).

Please replace the second paragraph on page 12 with the following rewritten paragraph:

The RNA biotinylation step involved the use of the HIGH-YIELD RNA LABELLING KIT® ~~High-Yield RNA Labelling Kit~~ (Enzo Diagnostics, NY, USA; P/N 900182) following the manufacturer's instructions. The following ingredients are mixed in an initial step:

22 µl aRNA

4 µl 10X HY reaction buffer,

4 µl 10X Biotin Labelled Ribonucleotides,

4 µl 10X DTT,

4 µl RNase inhibitor mix,

2 µl 20X T7 RNA polymerase.

Please replace the third paragraph on page 12 with the following rewritten paragraph:

The mixture is incubated at 37°C for 3-4 hours. The labelled aRNA is purified using RNEASY® ~~RNeasy~~ chemistry (Qiagen) following the manufacturer's instructions. The elution volume is 60 µl, 2 µl are used to determine the RNA concentration spectrophotometically by absorbance at 260 nm.

Please replace the sixth paragraph on page 13 directly under the heading Washing Procedure with the following rewritten paragraph:

The hybridization mix is removed from the probe array and set aside in a microcentrifuge tube. 280 µl 1X MES hybridization buffer is added to the chamber and a fluidics wash is performed on a GENECHIP® ~~GeneChip~~ Fluidics Station 400 using 6X SSPE-T buffer.

Please replace the third paragraph on page 14 under the heading AB stain (300 µl) with the following rewritten paragraph:

150 µl 2X MES hybridization buffer

146.25 µl water

3 µl BSA (50 mg/ml)

0.75 µl biotinylated antibody (500µg/ml) (Vector laboratories, P/N BA-0500)

The cartridge is incubated at 37°C for 30 minutes, the AB stain is replaced with 200 µl 1X MES hybridization buffer, and a fluidics wash is performed. After the wash step, the SSPE-T solution is removed, the chamber is filled with SAPE stain, and incubated at 37°C for 15 minutes. The SAPE stain is replaced with 200 µl 1X MES hybridization buffer and a fluidics wash is performed. The septa are covered with tape to prevent buffer leakage.

Microarrays are scanned on Affymetrix GENEARRAY® ~~GeneArray®~~ scanners. Raw data sets are normalized by scaling 75%- quantile of all probe sets of each chip to a target intensity of 200.

Please replace the fourth paragraph on page 14 directly under the heading Separation Method with the following rewritten paragraph:

Statistical analysis is performed with S-Plus (Insightful, Inc., USA) and GENESPRING® ~~GeneSpring~~® (Silicon Genetics, USA). Average difference values of less than 10 are rounded to 10. Low expression levels (between 10 and 50) are kept to ensure not to lose any possible pattern.

Please replace the third paragraph on page 16 with the following rewritten paragraph:

In GENESPRING® ~~GeneSpring~~™, each gene is normalized to itself by creating a synthetic positive control for that gene, which is the mean of all values of that gene in a dataset, and dividing all measurements for that gene by this positive control, assuming it is at least 0.01.

Please replace the paragraph header in the middle of page 16 with the following rewritten paragraph header: TAQMAN® Primer Probe Design

Please replace the fourth paragraph on page 16 directly under the paragraph header TaqMan Primer Probe Design with the following rewritten paragraph:

TAQMAN® ~~TaqMan~~ assays should be designed to the region of a gene that hybridizes to the corresponding probe set of the HG-U95Av2 microarray. This region is called target sequence. Using the NETAFFX® ~~Netaffx~~™ software (Affymetrix, Inc), the target sequence of a probe set is identified. The target sequence is then imported into the program PRIMER EXPRESS® ~~Primer Express~~ (Applied Biosystems), and the primer/probe selection is performed by the program with the following conditions:

Primer TM (melting temperature) should be between 58°C and 60°C. Optimally it should be 59°C, with a maximum TM difference of 2°C.

The primer GC (GTP,CTP) content should be between 20% at the minimum and 80% at the maximum, avoiding any 3' GC clamps.

Please replace paragraph seven on page 16 under the paragraph header TaqMan Primer Probe Design with the following rewritten paragraph:

The optimal primer length should be 20 residues, but can range form 9 to 40 residues.

The amplicon requirements should be that the minimum TM is 0°C, the maximum TM 92°C. The amplicon should have a minimal length of 50 residues, a maximal length of 150.

TAQMAN® ~~TaqMan~~ probe criteria are that the probe TM must be at least 0°C greater than the PCR primer TM, and the probe should not begin with a G (GTP) residue. If the target sequence is too short to identify any TAQMAN® ~~TaqMan~~ assay matching the above mentioned criteria, the sequence is aligned to the entire sequence of the gene (using standard software such as GCG, Wisconsin Package, Accelrys, San Diego, CA) and a longer stretch of DNA is selected, encompassing the target sequence. Sequences of the forward primer, reverse primer and the TAQMAN® ~~TaqMan~~ probe for each gene are listed in Table 4.

Please replace the Table 1 header on page 19 with the following rewritten Table 1 header:

Table 1: List of genes (with GENBANK® ~~GenBank~~ accession numbers) which are upregulated in pre-CR group

Please replace the Table 2 header on page 20 with the following rewritten Table 2 header:

Table 2: List of genes (with GENBANK® ~~GenBank~~ accession numbers) early downregulated in pre-CR group

Please replace the following Table 3 header on page 21 with the following rewritten Table 3 header:

Table 3: Subset of 10 genes from tables 1 and 2 with the most significant differential expression patterns for the pre-CR and the control group. The expression pattern of eight genes are validated by TAQMAN® ~~TaqMan~~™ real-time Q-PCR. nd: not done due to limited sequence information.

Please replace the Table 4 header on page 22 with the following rewritten Table 4 header:

Table 4: Sequences and labels of all probes and primers used in TAQMAN® ~~TaqMan~~™ assays